REMARKS

Claim 9 has been canceled. Claims 1-8 and new Claims 10- 17 remain active in the case. Reconsideration is respectfully requested.

Objection to Disclosure

The indicated paragraph on page 10 has been amended to correct the identification of the U.S. Patent called into question. (A copy of this patent is enclosed for the Examiners convenience.) Moreover, the U.S. Patent equivalent of the WO publication has also been provided. Entry of the amendments is respectfully requested.

Title of Invention

The application has been provided with an appropriate new title.

Claim Amendments

Several of the claims have been amended to correct and improve upon the syntax of the claims. Further, new Claims 10-17 have been added for which support can be found on pages 4-10 of the specification.

Statutory Rejection, 35 USC 112, 2nd Rejection

These grounds of rejection are obviated by the cancellation of Claim 9

Claim Rejection, 35 USC 112, 1st

Applicants do not concur with the Examiner's stated view that the present specification is only enabling with respect to a claimed combination of the lipopetide of formula (I) with Amphotericin B, Itraconazole, Nikkomycin X and Flucytosine 5-FC against *Aspergillus fumigatus*. It is pointed out that all of the embodiments of antifungal agents of

the present claims of widely differing chemical types are **known** antifungal agents, including the lipopeptide of formula (I), and as such the ways and means of formulating compositions containing these compounds into effective pharmaceutical compositions is well known and established. This is also obviously true of combinations of antifungal agents as indeed attested to by the cited and applied references, and in particular Franzot et al and '782 which describe the combination of a pneumocandin and other types of antifungal agents such as azoles, polyenes and the like. Further, all of the compositions disclosed have been tested against various fungal organisms as has been shown. Clearly, in view of what is known about the treatment of fungal organisms with known antifungal compositions, one of skill in the art, having the present specification in-hand, would be readily able to formulate composition embodiments within the scope of the present claims that would be effective against various types of fungal organisms. While there may be some one or few fungal strains that may not be as readily treatable with the present composition in comparison to others, such examples do not negate the present invention. Moreover, it is clear that in view of what is known in the prior art and what is described in the present specification, that no undue experimentation would be involved by one of skill in the art in determining how a given composition is to be formulated and tested for antifungal activity and effectiveness. Such experimentation is well within the capability of the skilled artisan. Accordingly, the enablement rejection is believed obviated and withdrawal of the same is respectfully requested.

Invention

The present invention is directed to a method of treating fungal diseases and a pharmaceutical composition to achieve this objective. The active formulation of the

invention is a combination of the lipopeptide compound [I] as set forth above and an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bacterial/permeability inducing protein product or polyoxin. The effect of the formulation of the invention is improved antifungal activity.

Claim Rejection, 35 USC 103

Claims 1-9 stand rejected based on 35 USC 103(a) as obvious over WO 98/10782 in combination with Franzot et al, Hector, U.S. Patent 5,030,619 or WO 96/ 11210. This ground of rejection is respectfully traversed.

It is clear that WO '782 discloses a combination therapy of known antifungal agents for the treatment of infectious diseases caused by various fungi. The reference is clearly relevant to the present invention as claimed because it discloses the combination of antifungal agents of a pneumocandin derivative of formula (I) of the reference with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bacterial/permeability inducing protein product or polyoxin. The effect of the formulation of the invention is improved antifungal activity. The pneumocandin derivative of formula (I) of the reference is related to but **not** the same as the cyclic hexapeptide component of the combination of the present invention as there are several structural distinctions between the present compound of formula (I) and the pneumocandin compound disclosed in the reference. This distinction is very important to the issue of patentability in this case, because as stated at the top of page 3 of the reference, while pneumocandins, as cyclic hexapeptides which function by inhibiting cell wall 1,3 -D-glycan synthesis, show potent activity against the likes of *Candida, Pneumocystis carinii and Aspergillus*, nevertheless the compound type shows weak activity with respect to *Cryptococcus* spp. This disclosure is consistent with the statement on page 3 of the present

text which states that previous studies evaluating the efficacy of lipopeptide compounds other than the lipopeptide of formula (I) of the present invention against *Cryptococcus neoformans* have shown these compounds to not have the effectiveness of the present compound of formula (I) against this type of fungal organism. However, the finding of the present invention is that the claimed combination of antifungal ingredients is effective against a variety of fungal types including *Cryptococcus*. This finding is not shown or suggested by '782.

The deficiencies of '782 are believed to be neither overcome nor improved by the disclosure of the cited WO document '210, because this document primarily is directed to the discovery that the lipopeptide compound of formula (I) of the present case is effective against the fungal strain of *Pneumocystis carinii*. A brief general statement is made in the reference that the compound is useful in the treatment of a subject infected with other classes of fungal pathogens, but no data of significance is provided showing the efficacy of the compound other than *Candida albicans* in an *in vitro* study. Accordingly, applicants submit that the disclosure of the '782 document does not bring the '782 document closer to the present invention.

The deficiencies of the above-discussed references are believed to be neither overcome nor improved upon by Franzot et al. This reference only discloses the combination of the specific Pneumocandin L-743,872 with Amphotericin B or Fluconazole as effective against *Cryptococcus neoformans* Pneumocandin L-743,872 is not either the cyclic hexapeptide that is employed in the combination of the present invention or the pneumocandin of the '782 reference. Accordingly, the Franzot et al reference does not bring the prior art closer to the present invention.

Finally, the Hector patent is believed to be of comparative secondary interest because it discloses the combination of a nikkomycin and an echinocandin B compound as having

antifungal effectiveness, especially against an infection of *Aspergillus*. This is consistent with the disclosure on page 3 of the '782 reference which mentions that echinocandins are related to pneumocandins and are antifungal agents. However, not only is the echinocandin of the reference not the cyclic hexapeptide of the present invention, but the reference only is directed to a composition which is effective against *Aspergillus*. There is no disclosure of effectiveness against *Cryptococcus*. Accordingly, the combined references do not suggest the invention as claimed and withdrawal of the rejection is respectfully requested.

It is now believed that the application is in proper condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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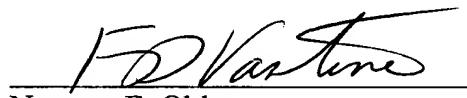

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